REMARKS

I. Status of the Claims

With entry of the above amendment, claims 14-21 and 23-26 are pending in this application and all claims are rejected by the Examiner. Claim 22 has been canceled. Applicants have amended claim 14 to incorporate the recited limitations of claim 22 regarding administration of adenovirus by "subretinal injection or intravitreous injection." Applicants reserve the right to pursue any canceled subject matter in a continuation application. Support for this amendment is found in the specification as filed, for example, in claim 22. Claims 19 and 25 have been amended to provide the full spelling of the abbreviations recited therein. One of skill in the art reading the specification and seeing the context of their use would understand what each of these standard abbreviations refers to. The claim dependency of claim 23 has been amended to reflect the amendment of claim 14 and cancellation of claim 22. No new matter has been added.

II. Claim Objections

Claims 19 and 25 are objected to for the use of the abbreviations "RDS", "NDI", and "MLP" as they allegedly "can represent various meanings", and the Office suggests spelling out the terms. Office Action, page 2. Although one of skill in the art reading the specification and seeing the context of their use would understand what each of these standard abbreviations refers to, claims 19 and 25 have been amended to provide the full spelling of the abbreviations recited therein. No new matter has been added.

III. The Claims Are Enabled Under 35 U.S.C. § 112, First Paragraph

Claims 14-26 are rejected under 35 U.S.C. § 112, first paragraph, because they allegedly contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to make or use the invention without undue experimentation. Office Action, pages 2-7. Specifically, the Office alleges that the "specification fails to provide adequate guidance and evidence for how to use a defective recombinant adenovirus expressing a protein or an antisense RNA to treat an eye disease or disorder, such as an ocular disease, via various administration routes so as to provide therapeutic effect in vivo." *Id.*, page 4. Applicants respectfully traverse the rejection.

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993); *see also* M.P.E.P. § 2164.04. The "invention" that must be enabled is that defined by the particular claim or claims of the patent or patent application. *See* M.P.E.P. § 2164; *see also Phillips Petroleum Co. v. U.S. Steel Corp.*, 673 F. Supp. 1278, 6 U.S.P.Q.2d 1065 (D. Del. 1987), aff'd, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989). This the Office has failed to do. Further, a claimed invention is enabled if one skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The Office cites Verma *et al.*, Nature 389:239-242 ("Verma"); Eck et al., Goodman and Gilman's The Pharmacological Basis of Therapeutics, pages 77-101 ("Eck); and Gorecki, Expert Opin. Emerg. Drugs, 6:187-109 ("Gorecki") and asserts the following reasons why it believes undue experimentation is required to practice the invention.

> The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reports that 'The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus, far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression'. (see page 239, right column).

Office Action, pages 4-5. The Office further states that:

> Eck et al., 1996...states that the fate of the DNA vector itself...,the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82).

Id., page 5.

First, Applicants submit that the disclosures of Verma, Eck, and Gorecki regarding the problems and obstacles to achieving efficacious or successful gene therapy are merely referring to safety considerations inherent in the clinical trial regulatory process generally, and are not addressing the enablement requirement of whether the skilled artisan could practice the specific methods recited in the claims without undue experimentation upon reading the specification. Evidence of the general

safety of gene therapies is not germane to the issue of enablement of the present claims.

Second, the Office has provided no basis for concluding that the relied-upon generalized problems with gene therapy would prevent the skilled artisan from practicing the method according to the invention for expressing a gene in at least one eye cell, comprising administering to at least one eye cell a defective recombinant adenovirus comprising an inserted gene. The experimental data in the specification clearly indicate successful delivery of a selected gene into cells of the eye with a defective recombinant adenovirus of the present invention. See, for example, page 15, entire page and especially lines 26-28, to page 16, lines 1-8; page 16, lines 14-22; and page 17, lines 21-23. No adverse reactions were observed in the experiments described in the specification. Page 3, lines 11-12. Expression of the gene was directly measured, and the extent of expression yielded intense staining. Id., pages 7-8. Expression was achieved in a highly cell-specific fashion. Id., pages 15-17. The alleged disadvantageous high immunogenecity of adenoviruses were not problematic here due, in part, to the fact that the eye is a privileged site.

And third, Applicants direct the Office's attention to further experimental work which validates the enabling disclosure of the Applicants' invention.

Bennett et al., Nature Medicine, 2:649-654 (1996) ("Bennett") describes altering the course of retinal degeneration in the *rd* mouse through subretinal injection of a recombinant replication-defective adenovirus that contains the murine cDNA for wild-type *βPDE*. A copy is enclosed ("Exhibit A"). The article states that subretinal injection of AD.CMVβPDE results in mRNA transcripts and protein activity, delaying

photoreceptor death by six weeks. Thus, Bennett reports ocular cell rescue by *in vivo* gene transfer with an adenovirus vector.

Genvec's public website at www.genvec.com has posted experimental results regarding *in vivo* injection of recombinant replication-defective adenovirus to an eye of a mammal and subsequent delivery and expression of a known neurotrophin, Pigment Epithelium-Derived Factor (PEDF). Applicants enclose copies of two separate Genvec studies ("Exhibit B"). The studies indicate that *in vivo* intravitreal injection of the Ad-PEDF is both efficacious and safe for treatment of ocular neovascular disease. Thus, Genvec reports efficient and safe ocular cell treatment by *in vivo* gene transfer of a neurotrophin with an adenovirus vector.

The methods disclosed in the Applicants' specification were used by Bennett and Genvec to reach their subsequent experimental results. Thus, the specification was enabling to those of skill in the art as of the filing date, as evidenced by the publication of Bennett and confirmed by the publications of Genvec particularly in regard to *in vivo* gene therapy. See MPEP § 2164.05(b). Accordingly, the rejection for lack of enablement is in error.

For the same reasons, Applicants' specification and examples also enable claim 20, wherein the gene encodes an antisense RNA molecule. For example, as discussed above, the experimental data in the specification clearly indicate successful delivery of a selected gene into cells of the eye with a defective recombinant adenovirus of the present invention. Selection, administration, and expression of numerous selected genes, including an antisense RNA molecule, are within the skill of the skilled artisan reading the specification. Accordingly, one of skill in the art reading the specification

would not require undue experimentation to practice the invention wherein the gene of the example, β-galactosidase, is replaced with another selected gene, such as a gene for an antisense RNA molecule.

In view of these remarks, Applicants submit that proposed amended claims meet the requirements of section 112, first paragraph. Reconsideration and withdrawal of the rejection is respectfully requested.

IV. The Claims Are Not Obvious Under 35 U.S.C. § 103

Claims 14-17, 21, and 24-26 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Stratford-Perricaudet, et al. J. Clin. Invest. 90:626-630 (1992), in view of Tsai et al., Arch. Opthalmol. 110:1167-1170 (1992). Office Action, pages 7-9. Claims 18-20 and 22-23 were not rejected as obvious.

Applicants respectfully traverse this rejection. In order to advance prosecution, however, Applicants have amended the claims to recite the limitation of claim 22 that "adenovirus is administered by subretinal injection or intravitreous injection." By its omission from the rejection, the Office indicates that claim 22 is NOT obvious in view of the cited references. All claims are dependent upon claim 14. Thus, entry of the amendment of claim 14, incorporating the limitation of claim 22, will render the obviousness rejection of claims 14-17, 21, and 24-26 moot.

V. Summary

In view of these amendments and remarks, Applicants submit that this case is in condition for allowance. Early notice to that effect is earnestly solicited.

Please grant any extension of time required to enter this response and charge any additional fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: April 13, 2004

By: _____
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